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Highly functionalized donor–acceptor cyclopropanes applied toward the synthesis of the *Melodinus* alkaloids

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Abstract

A series of highly substituted vinylcyclopropanes were prepared and examined as reaction partners in a palladium-catalyzed (3 + 2) cycloaddition with nitrostyrenes. Described herein are our efforts to synthesize an elusive 1,1-divinylcyclopropane by several distinct approaches, and to apply surrogates of this fragment toward the synthesis of the *Melodinus* alkaloids.

Keywords

Cycloaddition; Cyclopropanes; Stereoselective synthesis; *Melodinus* alkaloids; Claisen rearrangement

The *Melodinus* alkaloids are a class of dihydroquinolinone natural products related to the *Aspidosperma* alkaloids through an oxidative rearrangement of dehydrotabersonine (**1**, Scheme 1).[1,2] Despite their lack of known biological activity,[3,4] the structural complexity of the *Melodinus* alkaloids and the prospects of preparing non-natural derivatives for biological evaluation were both extremely appealing to our lab.

In the case of (+)-scandine (**3**),[1] (+)-meloscandonine (**4**),[5] and others,[6] three of the four contiguous stereocenters on the characteristic central cyclopentane ring are quaternary. To date, the only members of the family to have been synthesized are meloscine (**5**) and epimeloscine (**6**), both of which possess only two quaternary stereocenters on the central C ring.[7–9] It is hypothesized that (+)-scandine (**3**) is the biosynthetic precursor to the other *Melodinus* alkaloids.[2] Thus, we began to pursue the synthesis of scandine (**3**), which could allow access to the related dihydroquinolinone natural products.

[†]These authors contributed equally.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at XXXXXXXXXXXX.

Dedicated to Professor Harry H. Wasserman (1920–2013); a dear friend and mentor.

In planning a concise synthesis, we chose to exploit elements of symmetry found within the target natural product. In particular, the quaternary stereocenter at C(20) bears two olefinic substituents, and C(16) bears two carbon substituents in the carboxylic acid oxidation state. Accordingly, after disconnection of the E ring via benzylic C–H insertion, we envisioned that the D and B rings of **7** could be formed by substrate-controlled diastereoselective ring-closing metathesis and lactamization steps of divinylcyclopentane **8** (Scheme 2). This intermediate could arise, in turn, from nitrocyclopentane **9**, the product of a transition metal catalyzed, intermolecular formal (3 + 2) cycloaddition between a *trans*-β-nitrostyrene (**10)** and divinylcyclopropane **11**.[10]

At the outset of our synthetic efforts, we examined several possible approaches toward the synthesis of the desired divinylcyclopropane (**11**, Scheme 3). The geminal vinyl groups could potentially be installed through substitution of 1,1-dihalocyclopropane **12**,[11] itself generated from a dihalocarbene **13** and methylidene dimethylmalonate (**14**).[12] Alternatively, the two vinyl groups could be formed by elimination from cyclopropane **15**, derived from the reaction of olefin **17** with a malonate-derived carbenoid (**16**). Finally, we envisioned utilizing an S_N2' displacement of alkylidene cyclopropane **18** with a vinyl nucleophile. This cyclopropane could be synthesized from allene **19**.

We first examined the use of a 1,1-dihalocyclopropane (e.g. **12**) toward divinylcyclopropane **11** (Pathway A, Scheme 3). The synthesis and reactions of these building blocks have been extensively researched.[12] 1,1-Dihalocyclopropanes are known to react with dialkyl cuprates,[13] trialkyl zincates,[14] manganates,[15] or magnesates[16] to yield alkylated cyclopropylmetals, which can react with an electrophile to deliver products with geminal substitution. Furthermore, the cyclopropylmetal intermediates can be used in metal-catalyzed cross-coupling reactions with vinyl halides to deliver vinylcyclopropanes.[15]

Due to the highly reactive nature of methylidene dimethylmalonate (**14**),[17] we sought to first examine the vinylation of *gem*-dihalocyclopropanes using a reduced substrate. Accordingly, acrylate derivative **20** was prepared by a known procedure and protected as a silyl ether (**21**, Scheme 4).[18] Olefin **21** was then cyclopropanated using phase-transfer catalysis to afford *gem*-dibromocyclopropane **22**.

Unfortunately, efforts to directly vinylate cyclopropane **22** failed (Scheme 5). A Stille coupling with tetravinyltin was unsuccessful, as was the palladium-catalyzed cross coupling of the in situ-generated organomanganate with vinyl bromide.[15b] An attempt at a bis-alkynylation using Sonogashira coupling was also unfruitful. Since no desired substitution products were observed with this substrate, we did not pursue this route further and we shifted our focus to an alternative approach.

We turned our attention toward the formation of the desired vinyl groups by elimination of two leaving groups (Pathway B, Scheme 3). In this vein, we set out to prepare dimesylate **30** as a divinylcyclopropane precursor (Scheme 6). Baylis–Hillman reaction of methyl vinyl ketone (**25**) with acetaldehyde by a known procedure furnished adduct **26** which was then reduced to afford diol **27** as a mixture of diastereomers.[19] Although this substrate underwent mesylation cleanly, the product (**28**) was unstable as a neat oil, and underwent spontaneous,

rapid decomposition.[20] Furthermore, when a solution of the dimesylate in dichloromethane was subjected directly to cyclopropanation with diazodimethylmalonate, a complex reaction mixture was observed and no desired cyclopropane product (**30**) could be isolated.

To avoid problems of substrate stability, we opted to protect diol **27** as a disilyl ether (**31**, Scheme 7). This substrate was cyclopropanated efficiently using Du Bois' catalyst to give cyclopropane **32**, which was immediately subjected to alcohol deprotection under acidic conditions,[21] however, one hydroxyl group underwent an undesired lactonization to give bicyclic lactone **33**. This product was mesylated and eliminated to yield vinylcyclopropane **35**. Although an interesting structure, we were not able to advance lactone **35** to divinylcyclopropane diester **11**.

Finally, we examined a route to the divinylcyclopropane through S_N2' displacement of a substituted alkylidenecyclopropane (Pathway C, Scheme 3). De Meijere and coworkers have demonstrated that vinylcyclopropanes and methylenecyclopropanes with allylic leaving groups will react under palladium catalysis to form a common palladium allyl intermediate, which can then be alkylated.[22]

We sought to prepare an analogous alkylidenecyclopropane bearing the necessary methyl ester functionalities. Beginning with the known homoallenyl acetate **36**,[23] we screened cyclopropanation conditions using diazodimethylmalonate (**29**), examining several catalysts, carbenoid precursor equivalents, and addition times (Scheme 8). On our first attempt (entry 1), we were able to isolate the desired alkylidenecyclopropane (**37**) in 42% yield, although an excess of allene **36** was required. While using an excess of the diazo compound lowered the yield (entry 2), increasing the catalyst loading and the equivalents of the diazo improved the yield to 58% (entry 3). Increasing or decreasing the slow addition rate of the diazo reagent had a detrimental effect on the yield (entries 4 and 5). Changing the catalyst to the electron-poor trifluoroacetate complex resulted in a mixture of products (entry 6), and use of the electron-rich caprolactamate complex gave low conversion of the starting material (entry 7). Microwave heating of a neat mixture of the reaction components (entry 8) afforded considerably shortened reaction times, however, the yield was not improved. Finally, the use of Du Bois' catalyst ($Rh_2(esp)_2$) gave the highest isolated yield (80% yield, entry 9), with a short reaction time, low catalyst loading, and no need for syringe-pump addition of the diazodimethylmalonate.[24]

With the desired alkylidenecyclopropane **37** in hand, we examined an array of allylic substitution conditions with vinyl nucleophiles, including those reported by de Meijere,[22] as well as other catalytic systems with vinyl alanes and cuprates (Scheme 9). Unfortunately, in all cases, none of the desired divinylcyclopropane **11** was observed, and only ring-opened products were obtained.[25,26] It is possible that the diester functionality serves to weaken the distal bond of the methylenecyclopropane, favoring ring-opening rather than substitution. We did find, however, that we could smoothly remove the acetate protecting group through a two-step procedure from homoallenyl acetate **36** to furnish primary allylic alcohol **38** in 94% yield (Scheme 10).

At this stage, we considered that the use of a Claisen rearrangement might offer an alternative pathway to install the desired quaternary carbon on the cyclopropane (Scheme 11a).[27] The use of Claisen rearrangements to install vicinal quaternary centers is well precedented.[28] Furthermore, the relief of ringstrain (i.e., from alkylidenecyclopropane to cyclopropane) was predicted to aid the efficiency of the C–C bond formation. However, we envisioned potential chemoselectivity and side-reactivity problems in the conversion of Claisen product **40** to the desired divinylcyclopropane (**11**). Particularly, conditions would be necessary that could reduce the product carbonyl in the presence of the methyl esters and prevent concomitant lactonization.

Accordingly, we turned to the Eschenmoser–Claisen reaction, since numerous examples exist in the literature for chemoselective reduction of amides in the presence of esters,[29] and the resulting tertiary amines (**42**) would not be expected to react with the pendent ester functionalities and can be converted to olefins by means of the Cope[30] or Hofmann[31] elimination (Scheme 11b).

We therefore treated alcohol **38** under typical reaction conditions with dimethylacetamide dimethyl acetal, and observed the formation of amide **43** in moderate yield (Scheme 12).[32] The main side product of the reaction was conjugated amide **44**, likely formed by base-promoted ring opening of the desired product, and extensive screening of reaction temperatures and times could not improve the yield of the desired vinylcyclopropane **43**. Amide **43** was reduced with alane to dimethylamine **45** in 36% yield. Efforts to eliminate the amine (**45**) to form the desired divinylcyclopropane (**11**) have been unsuccessful to date. Fortunately, our efforts to this point provided three unique vinylcyclopropanes (**35**, **43**, and **45**) which we could examine in the palladium-catalyzed (3 + 2) reaction.

With three highly functionalized vinylcyclopropanes in hand, we set out to determine their compatibility with palladium-catalyzed (3 + 2) cycloaddition conditions originally developed by Tsuji.[10] Under an array of conditions, no cyclopentane products could be isolated (Scheme 13). In the case of dimethylamide substituted cyclopropane **43**, the starting material was isomerized in high yield to conjugated amide **44** as a mixture of olefin isomers. Dimethylamine analogue **45** and bicyclic vinylcyclopropane **35** showed no reactivity, even at elevated temperatures.

The isomerization of dimethylamide **43** is attributed to the presence of acidic protons on the substrate: upon formation of the palladium(II) allyl species (**48**), the pendant malonate acts as a base, eliminating Pd(0) via deprotonation to give conjugated amide **44** (Scheme 14).

As for vinylcyclopropanes **35** and **45**, we propose that the lack of reactivity results from a demanding allylation step of the catalytic cycle (Scheme 15). Whereas hard nucleophiles such as Grignard reagents typically add to the more highly substituted terminus of the allyl fragment under palladium catalysis via an inner-sphere mechanism, soft nucleophiles often attack at the least-substituted position through an outer-sphere mechanism. In the case of an unsubstituted vinylcyclopropane (3 + 2) cycloaddition (*i.e.* **49**, R = H), conformational effects in the ring closure presumably override this innate selectivity, resulting in addition to the more highly substituted internal position of the allyl fragment. However, in the case of

our substituted vinylcyclopropanes (*i.e.* R ≠ H), the steric demand is possibly too high to form the desired cyclopentane product (**50**) under these conditions.

In the course of our studies, Curran and Zhang completed the total syntheses of (±)-meloscine (**5**), (±)-epimeloscine (**6**), and several unnatural analogs by a route similar to our own original strategy (Scheme 16).[7d,7i] They were able to construct necessary divinylcyclopropane **55** through a tandem oxidation-Wittig methylenation sequence from cyclopropane **53**. After coupling of acid **55** with aniline **57**, the core tetracycle **59** was formed via an intramolecular radical-mediated cycloaddition and quickly advanced to epimeloscine (**6**) and meloscine (**5**). Scandine (**3**), the parent of the natural product family, was not accessed via this route but the similarity of their approach to our own original pathway, as well as the challenges we faced in effecting a transition metal catalyzed intermolecular (3 + 2) cycloaddition encouraged us to modify our synthetic plan.

The primary revision to our retrosynthesis involves using a monovinylcyclopropane (**63**) in the palladium-catalyzed (3 + 2) cycloaddition, and appending the second vinyl group at a later stage by C–H functionalization (Scheme 17).

In 2011, we disclosed our progress toward scandine, using the palladium-catalyzed intermolecular (3 + 2) cycloaddition strategy as planned in our revised retrosynthesis (Scheme 18).[33] We were able to synthesize monovinylcyclopropane **63** from dimethylmalonate (**64**) and dibromide **65** via a known procedure.[34] The subseuqent palladium-catalyzed (3 + 2) cycloaddition of cyclopropane **63** and nitrostyrene **47** proceeded smoothly. Tandem reduction and lactamization provided tricycle **67** as a 2:1 mixture of diastereomers at C(20) in favor of the undesired stereoisomer. Nevertheless, after reductive amination, acetylation, and ring-closing metathesis, we were able to access the tetracyclic ABCD ring system of the *Melodinus* alkaloids (**72**) in only six steps from commercial sources.

In summary, efforts to synthesize and apply a 1,1-divinylcyclopropane toward the total synthesis of scandine are described. Furthermore, we have applied a monovinylcyclopropane toward the preparation of a tetracyclic precursor to scandine via a palladium-catalyzed (3 + 2) cycloaddition. The remaining challenges to overcome in the synthesis include E ring closure by benzylic C–H insertion and installation of the C(20) vinyl group. Finally, the derivatization of scandine to other members of the natural product family will be examined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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26. Other leaving groups were examined including diethylphosphate and mesylate. Neither compound could be successfully advanced to the desired divinylcyclopropane.
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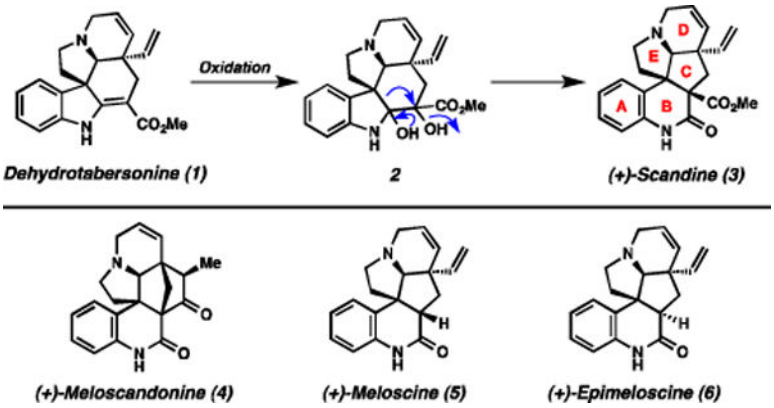
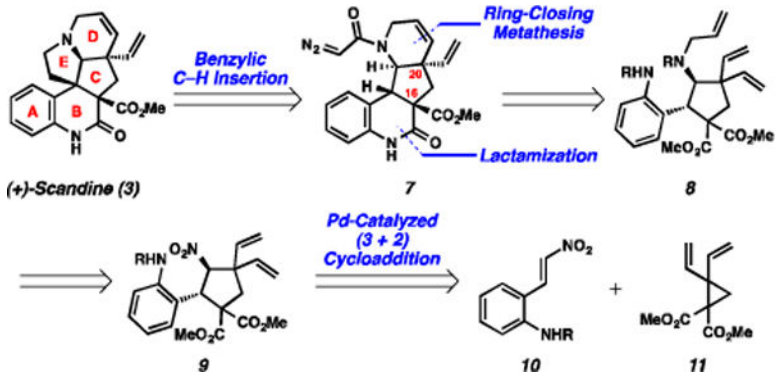
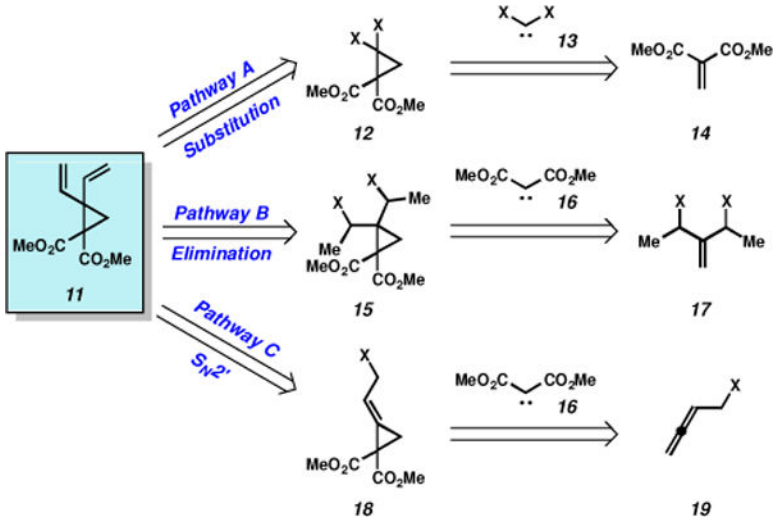


Scheme 1.
Proposed biosynthesis of the *Melodinus* alkaloids.

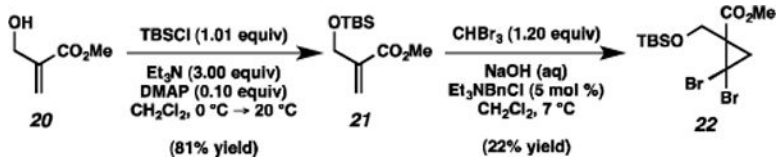


Scheme 2.
Retrosynthetic analysis of scandine (**3**).



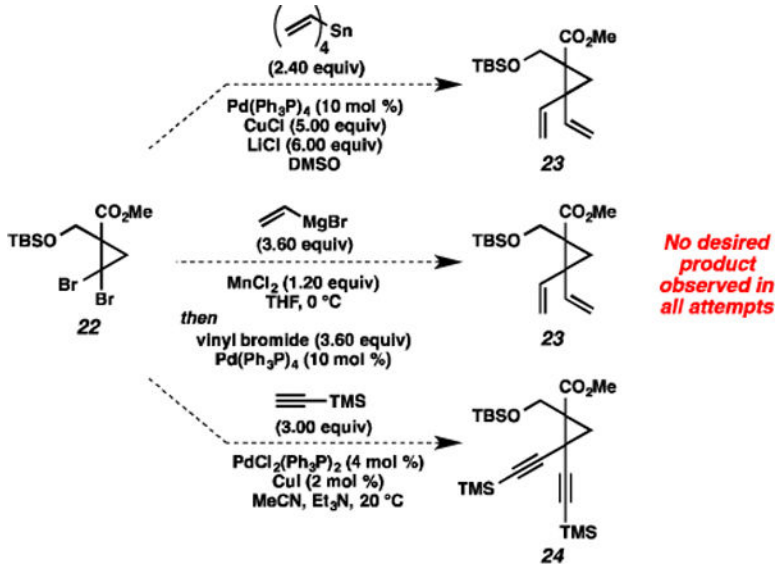
Scheme 3.

Retrosynthetic analyses of cyclopropane **11**.



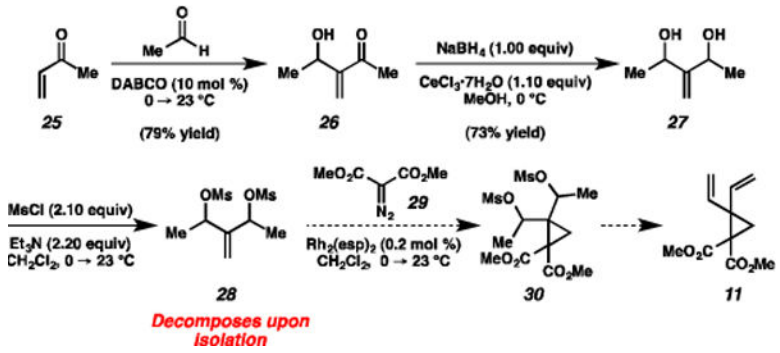
Scheme 4.

Synthesis of reduced *gem*-dihalocyclopropane **22**.



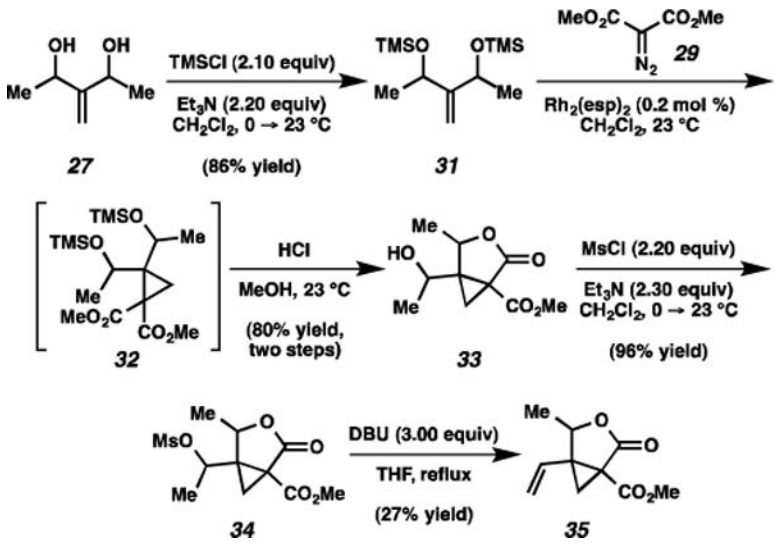
Scheme 5.

Efforts to substitute dibromocyclopropane **22**.



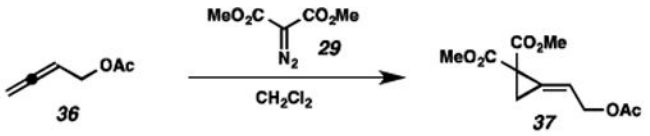
Scheme 6.

Synthetic approach to elimination substrate **30**.



Scheme 7.

Vinylcyclopropane synthesis via diol **27**.

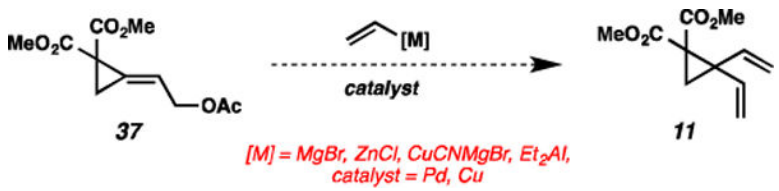


Entry	Diazo Equiv	Catalyst	Temperature	Addition Time	Yield (%)[a]
1	0.30	$Rh_2(OAc)_4$ (0.25 mol %)	reflux	8 h	42[b]
2	2.00	$Rh_2(OAc)_4$ (0.25 mol %)	reflux	6 h	28[b]
3	3.00	$Rh_2(OAc)_4$ (1 mol %)	reflux	6 h	58
4	3.00	$Rh_2(OAc)_4$ (1 mol %)	reflux	12 h	37
5	3.00	$Rh_2(OAc)_4$ (1 mol %)	reflux	3 h	38
6	3.00	$Rh_2(tfa)_4$ (1 mol %)	reflux	3 h	18
7	3.00	$Rh_2(cap)_4$ (1 mol %)	reflux	3 h	22[c]
8	1.30	$Rh_2(OAc)_4$ (0.4 mol %)	100 °C[d]	–	51
9	1.30	$Rh_2(esp)_2$ (0.1 mol %)	0 → 23 °C	–	80[b]

[a] ^{1}H NMR yield (pentachlorobenzene as internal standard). [b] Isolated yield. [c] 55% recovered starting material. [d] Microwave heating, solvent-free, 15 minute reaction time.

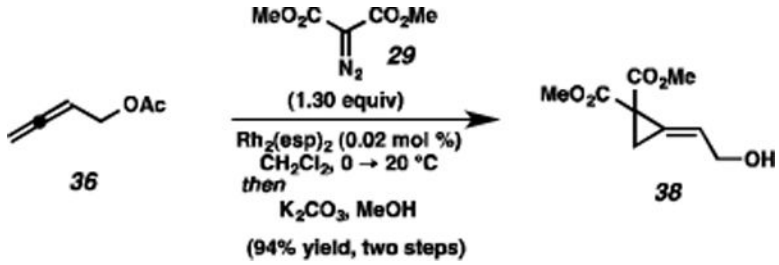
Scheme 8.

Cyclopropanation of homoallenyl acetate **36**.



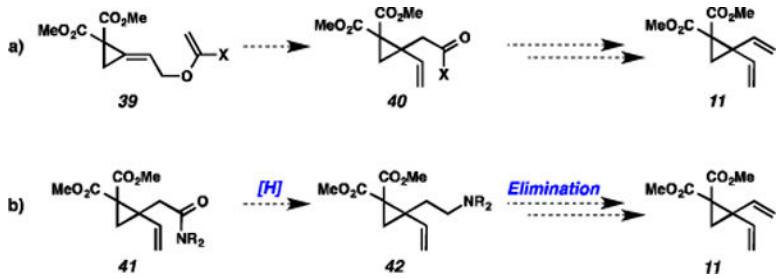
Scheme 9.

Attempted vinylation of diester cyclopropane **37**.

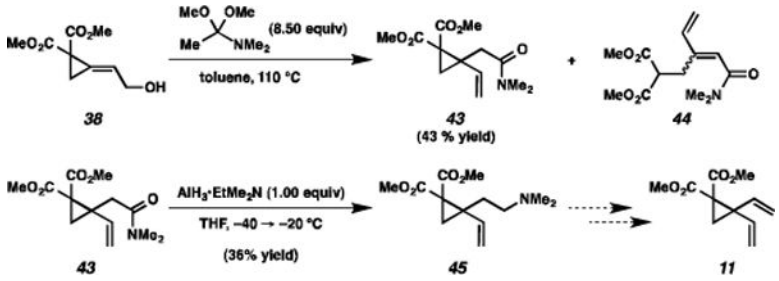


Scheme 10.

Synthesis of primary allylic alcohol **38**.

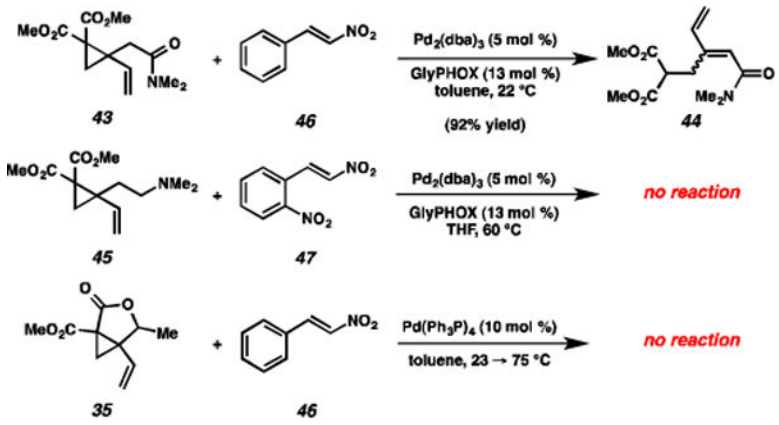


Scheme 11.
Proposed Claisen rearrangement routes.



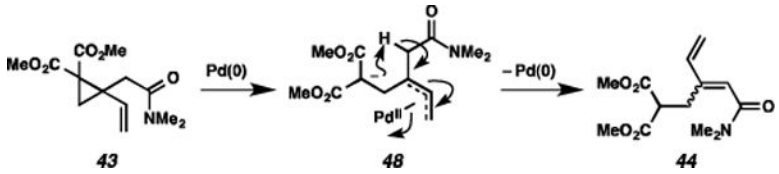
Scheme 12.

Eschenmoser-Claisen rearrangement of **38**.



Scheme 13.

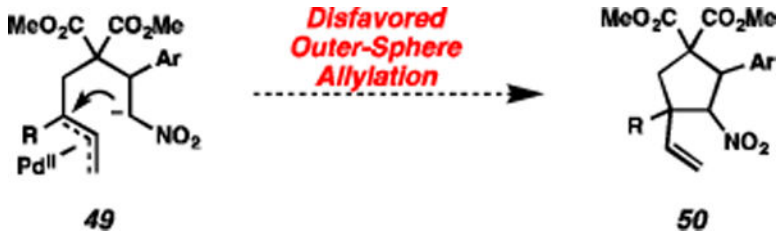
Palladium-catalyzed (3 + 2) cycloaddition attempts.



43 48 44

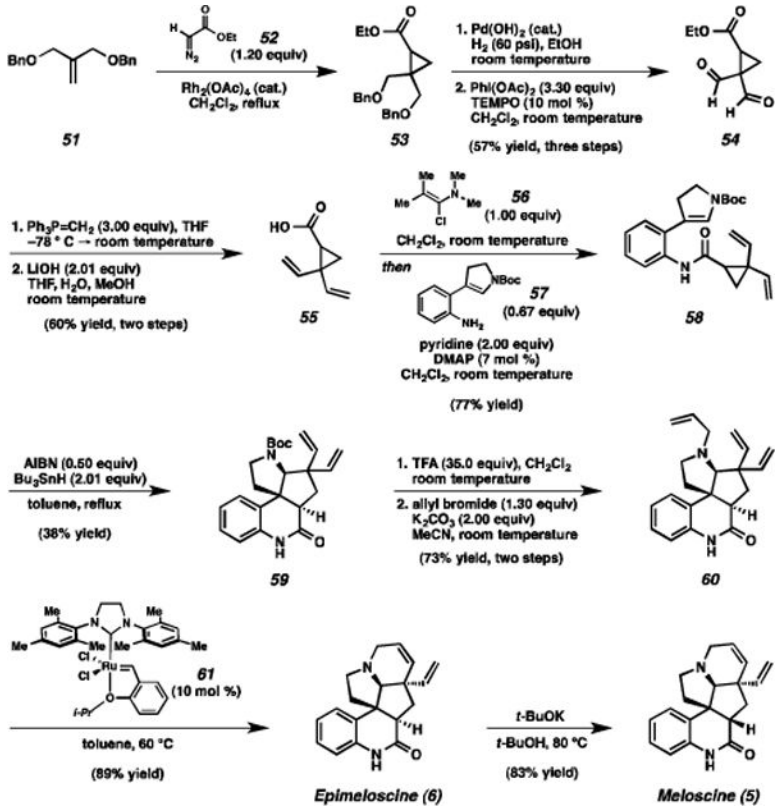
Scheme 14.

Mechanistic rationale for the formation of amide **44**.



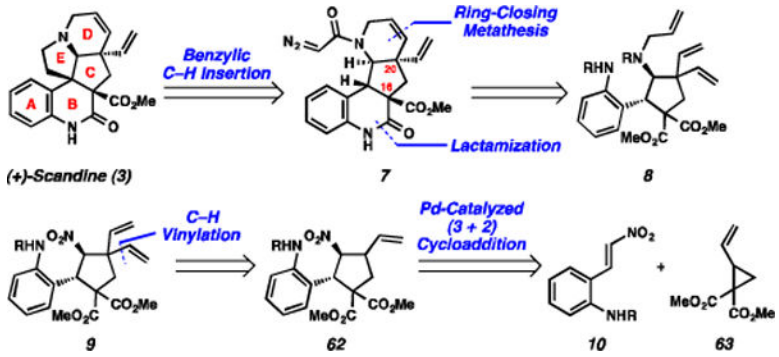
Scheme 15.

Rationale for the lack of desired reactivity of highly substituted vinylcyclopropanes.

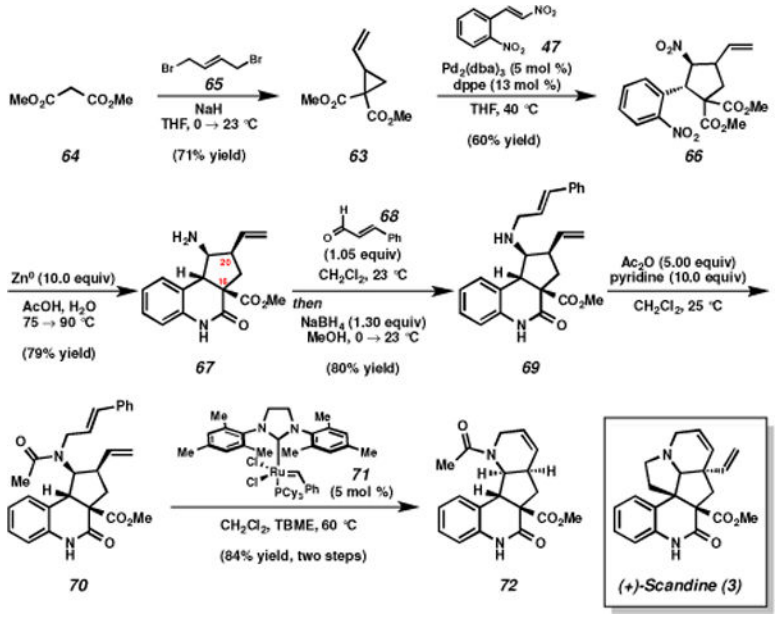


Scheme 16.

Total syntheses of epimeloscine and meloscine by Curran and Zhang (ref. 7d).



Scheme 17.
Revised retrosynthetic analysis.



Scheme 18.
Assembly of the ABCD ring system.